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Studies of Conformational Equilibria and Equilibration by Nuclear Magnetic Resonance Spectroscopy[1]

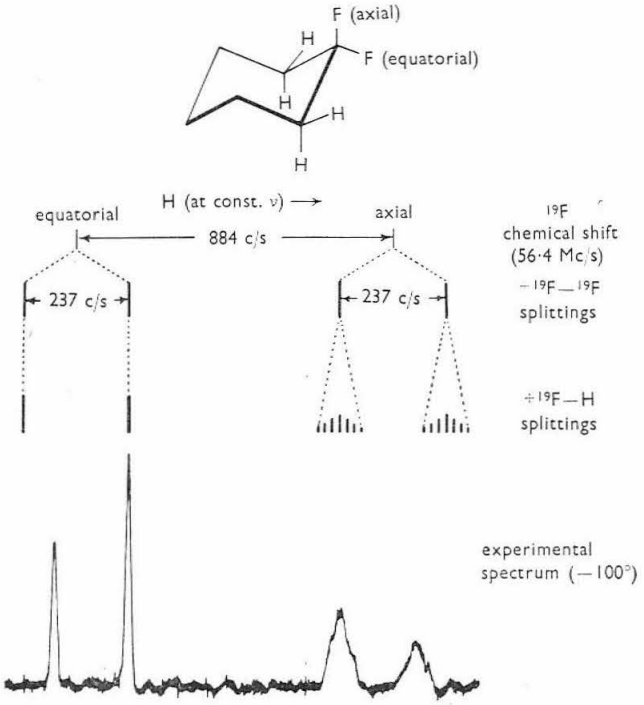
The study of conformational equilibria and equilibration by nuclear magnetic resonance in cyclic compounds has been found to be considerably facilitated by use of ^{19}F *spectra of* gem-*fluoro derivatives. Results obtained with cyclohexane,* cis-*decalin, and cycloheptane ring systems were reviewed with particular emphasis on the degree with which conclusions drawn might also be applicable to the parent cyclic hydrocarbons.*

This article is based on The Chemical Society Centenary Lecture given by Professor Roberts at Glasgow, Manchester, London and East Anglia.

NUCLEAR MAGNETIC resonance spectroscopy has been extraordinarily fruitful in the study of stereochemical problems, especially those associated with conformational analysis. In reasonably favourable cases, the position of the equilibria between conformational isomers can be determined with a high degree of accuracy and, in many cases, it is also possible to make measurements of rates of equilibration of such isomers as a function of temperature. The activation parameters obtained from such measurements are of special theoretical interest because the rate processes involved are not complicated by making and breaking of bonds. This, along with the well-established utility of conformational analysis in natural-product chemistry, has led to much research on conformations and conformational equilibration in a variety of acyclic and cyclic compounds. Many of the principles which are involved are to be illustrated here using examples drawn from work in our own laboratories. There will be no attempt to provide a general review of either conformational analysis or n.m.r. spectroscopy. The lack of reference to many studies of other workers of conformational equilibration should not be interpreted as a claim for priority or originality of the ideas and concepts employed here. Eliel[2a] and Feltkamp and Franklin[2b] have provided excellent reviews which give a more balanced perspective of the development of this area of research.

A salient feature of the studies to be described here is the emphasis on the use of the ^{19}F resonance spectra of *gem*-substituted difluorocycloalkanes as an aid to conformational analysis. The hope has been to have the fluorines act as a sort of tracer or label for hydrogen, with advantage to be taken of the ten to 50 times greater chemical shift of fluorine with respect to hydrogen. The validity of the assumption that fluorine might be a reasonable equivalent of hydrogen in conformational problems will be discussed in some detail later. The advantages of fluorine for studies of this kind are well illustrated by the spectrum of 1,1-difluorocyclohexane under conditions where ring inversion is slow (Fig. 1).[3] The elements of this spectrum, reading down from the top of Fig. 1, are: first, a chemical-shift difference between the axial and equatorial fluorines of 884 c/s at 56·4 Mc/s; then, a fluorine–fluorine spin–spin splitting of 237 c/s; and finally, hydrogen–fluorine splittings, assumed here to involve only the four vicinal hydrogens, which are shown as being larger for one of the fluorines than the other. The available theoretical and experimental evidence agree in having the axial fluorines more strongly coupled with the adjacent hydrogens and, in fact, the difference between these couplings is a convenient diagnostic tool for determining which of a pair of appropriate fluorine resonances on a cyclohexane ring should be taken

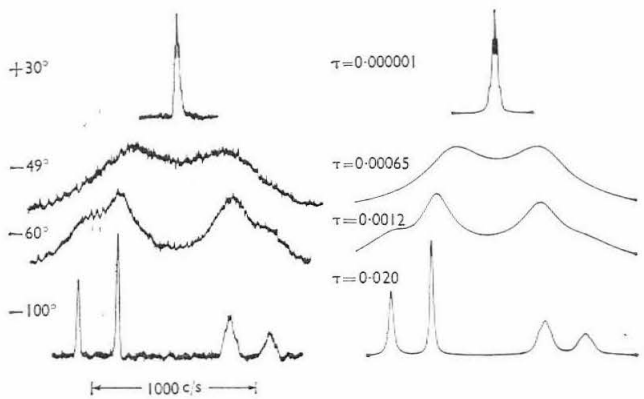
FIG. 1. Chemical shift and spin–spin splitting in ^{19}F spectra of 1,1-difluorocyclohexane at −100°.



as arising from axial or equatorial fluorines. It is noteworthy that the *whole* breadth of the chemical-shift difference and couplings between an axial proton and an equatorial proton located on the same carbon is normally substantially less than the breadth of just *one* of the broadened peaks of an axial fluorine.

A very special feature of the experimental spectrum of 1,1-difluorocyclohexane shown in Fig. 1 is that it was taken at −100°. Between −100° and 30°, the spectrum changes dramatically as shown in the left side of Fig. 2.[3]

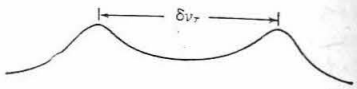
FIG. 2. Experimental (left) and calculated (right) ^{19}F spectra of 1,1-difluorocyclohexane as a function of inversion frequency. Each of the calculated spectra is labelled with the appropriate τ which is the mean lifetime in seconds before inversion occurs.



The change in spectrum with increasing temperature is, of course, due to an increase in the rate of ring inversion and, on the right side of Fig. 2, are shown theoretical spectra which utilize chemical shift and coupling parameters determined at −100° but which were calculated with different values of τ, the mean lifetime of the molecules in seconds, before inversion occurs. Comparison of theoretical and experimental spectra of these kinds permit evaluation of τ as a function of temperature and from this the activation parameters for rate processes involved.

It has been common to use peak separations below the so-called 'coalescence point' (*i.e.* below −46° for 1,1-difluorocyclohexane, Fig. 2) to obtain τ values with the

$$\frac{\delta\nu_\tau}{\delta\nu_\infty} = \left[1 - \frac{1}{2\pi^2\tau^2(\delta\nu_\infty)^2}\right]^{1/2}$$



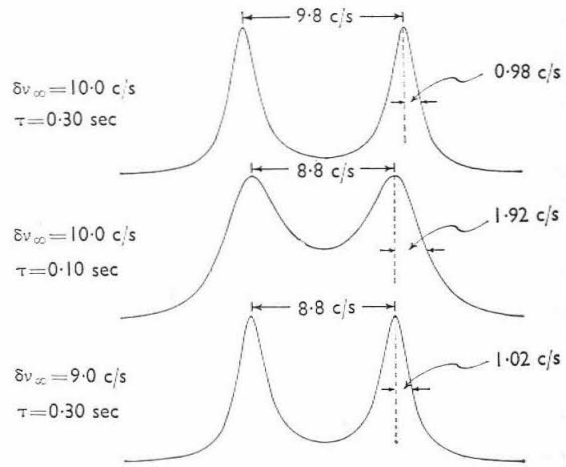
τ = mean lifetime of each state

$\delta\nu_\infty$ = chemical shift when $\tau = \infty$

Valid for: equal populations, spin coupling absent, no overlap of lines at $\tau = \infty$, $\delta\nu_\infty$ constant.

aid of the Gutowsky equation above. When τ is to be determined as a function of temperature, this procedure is not valid unless $\Delta\nu_\infty$ is independent of temperature. A much more reliable measurement is of the line shape because, as can be seen from Fig. 3, the line shape is more sensitive to changes in τ and less sensitive to changes in $\Delta\nu_\infty$ than is the peak separation. In the work to be described here, line shapes were calculated by the method of Alexander.[4]

FIG. 3. Typical differences produced in theoretical spectra by changes in $\delta\nu_\infty$ and τ. The top spectrum is the standard. The middle spectrum has the same $\delta\nu_\infty$ but a smaller τ. The line separation for this spectrum is 8·8 c/s which is the same as for the bottom spectrum wherein τ is as in the top spectrum but $\delta\nu_\infty$ has been decreased to 9·0 c/s. The point is that a decrease in τ produces a much larger change in line width than does a change in $\delta\nu_\infty$.



For all curves T_2=0·32 sec, J=0·0 c/s

TABLE I

REPORTED ACTIVATION ENTHALPIES FOR INVERSION OF CYCLOHEXANE AND FLUORINATED CYCLOHEXANES

	ΔH^*(kcal/mole)	Investigator
C_6H_{12} ..	11·5	Jensen *et al.*
	9·0	Harris and Sheppard (1961)
	11·5 (spin echo)	Meiboom
	10·9	Anet *et al.*
	10·5	Bovey *et al.*
	10·3	Harris and Sheppard (1964)
	9·1 (spin echo)	Gutowsky
$C_6H_{11}F$ ..	9·6	Bovey *et al.*
$C_6H_{10}F_2$ ..	11·6 (CH_2Cl_2)	K. Nagarajan
	10·9 (propene)	S. Spassov
	9·5 (CS_2)	Gutowsky *et al*
	9·1 ($CFCl_3$)	,, ,,
	9·8 (spin echo)	,, ,,
C_6F_{12} ..	9·9	Tiers

Values for the activation energy for inversion of cyclohexane and fluorinated cyclohexanes have been obtained by a number of workers starting with Jensen and his co-workers[5] in 1960 (see Table I). In general, the agreement between different workers is satisfactory, especially considering that quite different procedures were used to evaluate τ. Of particular importance to the story here is the close similarity between the activation energies determined for cyclohexane and fluorocyclohexanes. It is evident that substitution of fluorine for hydrogen results in, at most, a small decrease in the activation energy for inversion. Such a decrease is to be expected because each chair conformation will have axial fluorine–hydrogen interactions which would be expected to make the ground states slightly less stable relative to the transition state for inversion. The same kind of effect on E_a is observed with other substituents as can be seen from the activation parameters given in Table II for several substituted *gem*-fluorocyclohexanes which have been studied by following the temperature dependence of their fluorine spectra.[3]

The fluorine-labelling technique is useful for studying conformational equilibria and, in general, the ^{19}F chemical-shift differences observed at room temperature with various 4-substituted-1,1-difluorocyclohexanes (see Table III)[3] correspond in a reasonable way to what is already known of the effects of substituents on conformational equilibria.[2] There are several aspects of the results given in Table III which are worthy of comment. In the first place, we note that there is only a very small temperature dependence of the fluorine chemical-shift difference with a 4-t-butyl group between 35° and −100°. This is in agreement with the idea that the t-butyl group will be very predominantly in the equatorial position. With a 4-methyl group, the temperature effect on the chemical-shift difference is larger and, if we assume that at −100° the methyl group is solely equatorial, the change in going to room temperature corresponds to an equilibrium mixture containing about 5 per cent of the form with methyl axial. The 3-methyl is different from 4-methyl group in having

TABLE II

ACTIVATION ENERGIES FOR SOME *GEM*-FLUOROCYCLOHEXANES

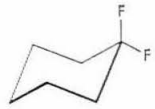
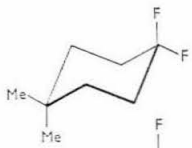
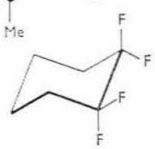
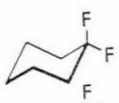
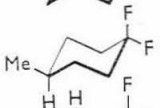
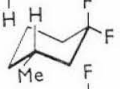
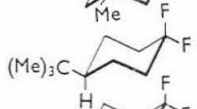
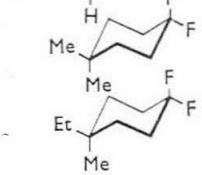
	Solvent	E_a(kcal/mole)	A
	propene	10·9 ± 0·5	$6·2 \times 10^{13}$
	propene	9·4 ± 0·5	$9·1 \times 10^{11}$
	propene	8·0 ± 0·3	$1·5 \times 10^{10}$

TABLE III

CHEMICAL SHIFTS AND COUPLING PARAMETERS IN ^{19}F-SPECTRA OF ALKYL-SUBSTITUTED *GEM*-FLUOROCYCLOHEXANES

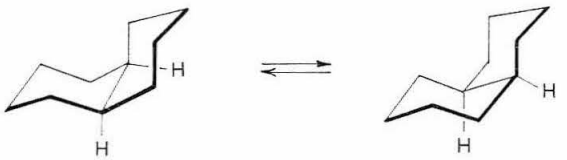
	30°		~−100°	
	δ_{F-F} c/s	J_{F-F} c/s	δ_{F-F} c/s	J_{F-F} c/s
	0	0	884	237
	563	238	610	238
	697	239	713	239
	661	236	671	236
	0	0	653	235
	154	234	696 (55%) 642 (45%)	235 235

a much smaller temperature dependence of the fluorine chemical shift but this is explicable in terms of the expected 3-methyl–fluorine interaction when the methyl group is axial which would not occur with an axial 4-methyl group.

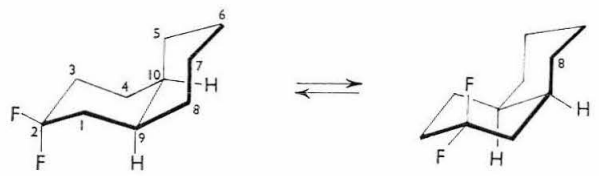
What may be a very important effect with far-reaching implications is the much smaller chemical-shift differences observed with the substituted *gem*-fluorocyclohexanes than with 1,1-difluorocyclohexane itself.[6] The most reasonable explanation is in terms of a distortion of the ring produced

by the substituent groups. This explanation is strongly supported by results obtained with *cis*-decalin derivatives as will be described later.[7] However, what we do not know yet is the degree of sensitivity of the fluorine chemical shifts to distortion of the ring. The *cis*-decalin results to be discussed below suggest that the sensitivity is likely to be very large and, if so, then these fluorine chemical-shift differences may turn out to be very helpful for diagnosis of subtle conformational effects. What is needed is independent measurement of the postulated ring distortion and a calibration curve of some angular measure of ring distortion against ^{19}F chemical-shift differences. The absolute values of the chemical shifts may also be significant in this connexion; however, this possibility will be discussed elsewhere.

The fluorine-labelling technique is particularly valuable for the study of conformational equilibration in the chair–chair interconversion of *cis*-decalin.[9,10] With *cis*-decalin itself, the two forms are enantiomers and are therefore energetically equivalent. The situation is quite different

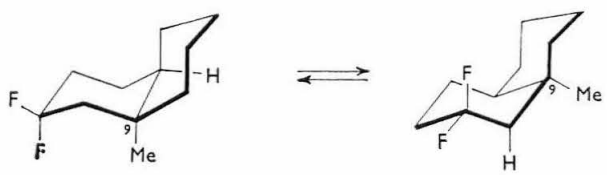


for 2,2-difluoro-*cis*-decalin where the forms I and II are not expected to be equally probable because of the way axial fluorine interacts with the hydrogens at 8-position in form II but not in form I. This leads to the expectation that, at low enough temperatures for interconversion to be slow, two separate AB patterns should be observed corres-



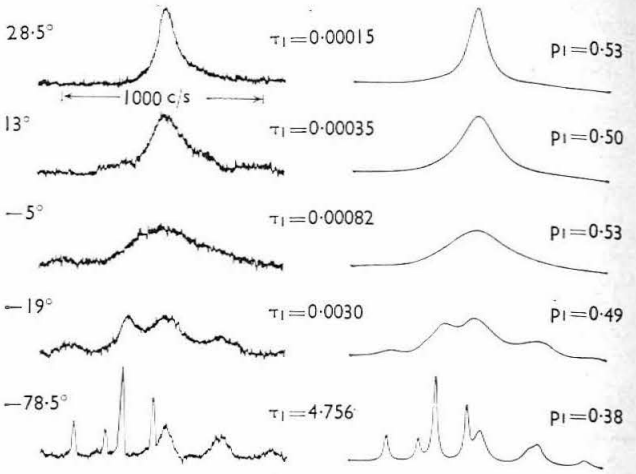
I II

ponding to I and II with the one representing I in greater concentration. When interconversion is fast, an average AB pattern is expected. Fig. 4 shows the way the fluorine spectrum of 2,2-difluoro-9-methyl-*cis*-decalin actually changes with temperature. At the lowest temperature, two AB spectra are clearly evident with axial and equatorial types of resonances. For this compound, the proportions of the forms III and IV are nearly but not exactly equal at −78·5°. The spectra are substantially blurred at the higher temperatures by rapid ring inversion.



III IV

FIG. 4. Experimental and calculated changes in line shape for inversion in the ^{19}F spectrum of 2,2-difluoro-9-methyl-*cis*-decalin. The values given for p_1 correspond to the mole fraction of the conformation III.



Calculation of theoretical spectra for this kind of system is much more complex than for cyclohexane inversion as shown in Fig. 4 because four chemical shifts, two coupling constants, four relaxation times, and the equilibrium constant for I ⇌ II must be taken into account along with τ. Theoretical curves calculated with the aid of the Gerig[4] programme will be seen to reproduce the experimental spectra well. In these calculations, both τ and p, the proportion of isomer I (R = CH_3, R′ = H), was varied until a satisfactory fit was obtained. The data obtained in this way[10] for a number of 2,2-difluoro-*cis*-decalin derivatives are summarized in Table IV.

The activation energy for the conversion of I to II for 2,2-difluoro-*cis*-decalin was found to be 14·6 kcal. Detailed calculations[10] by the Hendrickson-Wiberg procedure[11] of the energies of various conformations which might be intermediate in this interconversion suggest an activation energy of about 17 kcal/mole which is reasonably close to the experimental value. The activation energy for inversion

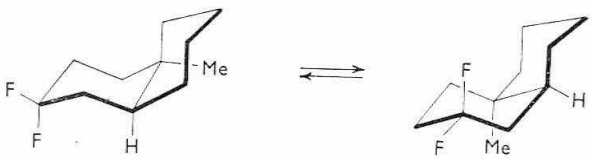
TABLE IV

EQUILIBRIUM CONSTANTS, MAGNETIC RESONANCE SHIFTS AND COUPLINGS, AND ACTIVATION PARAMETERS FOR INTERCONVERTING CONFORMERS OF 2,2-DIFLUORO-*cis*-DECALINS

2,2-difluoro-decalin	$K=\frac{I}{II}$, 30°	δ_{AB} (c/s)	J_{AB} (c/s)	E_a (kcal/mole)	δ'_{AB} (c/s)	J'_{AB} (c/s)	E'_A (kcal/mole)
cis-	2·9	757	233	14·6 ± 0·7	334	239	13·9 ± 0·7
cis-9-methyl-	1·08	544	239	9·1 ± 0·6	397	242	9·2 ± 0·6
cis-10-methyl-	3·4	713	235	10·6 ± 0·6	188	233	10·4 ± 0·6
cis-9-ethyl-	1·00	558	239	9·5 ± 0·5	549	236	9·5 ± 0·5

The unprimed values are for the conformation which corresponds to I and the primed values for the information which corresponds to II.

is substantially reduced by substitution of alkyl groups at the 9- or 10-positions of *cis*-decalin. This appears to be a consequence of a substantial degree of destabilization of the ground state of the *cis*-decalin ring system by the axial-alkyl against *syn*-axial hydrogen interactions which occur in a 9- or 10-alkyl substituted *cis*-decalin in either conformation (III or IV and V or VI)—the point being that the alkyl



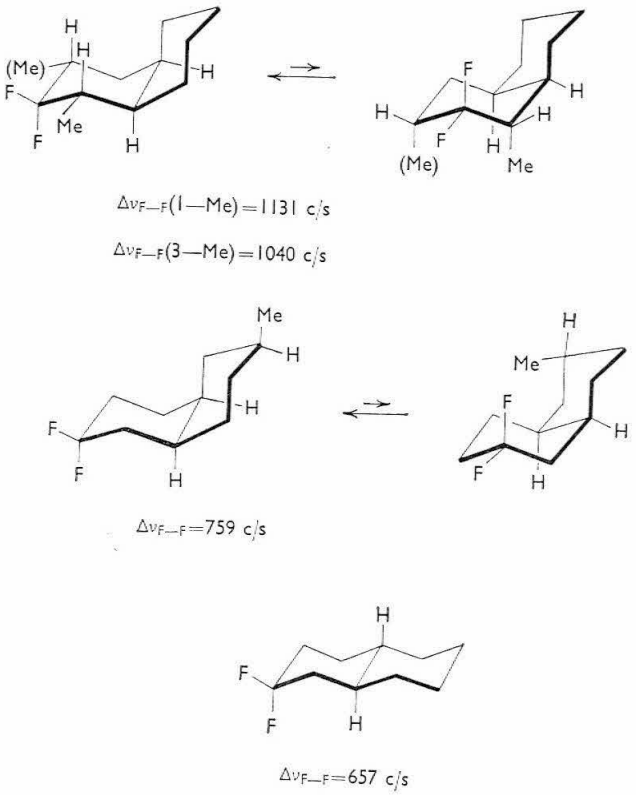
V VI

group must be axial to one or the other of the rings in all of these forms. The ascribing of the afore-mentioned abnormal fluorine chemical shifts to some degree of ring distortion is in general accord with the shifts observed with III–VI. A 10-methyl group as expected has a negligible effect on the equilibrium between V and VI and a relatively small effect on the equatorial-axial chemical-shift difference of the fluorines in V. However, the corresponding chemical shift for VI is profoundly affected, being only 188 c/s as compared to 761 c/s in I. This is in accord with the idea that the axial-fluorine against ring interaction in II produces a distortion leading to the chemical-shift difference decrease of 347 c/s and the additional interaction of the axial-methyl against the *syn*-hydrogens at the 1,3-positions in VI further increases the distortion in the neighbourhood of the fluorines and their chemical-shift difference.

Somewhat different effects are observed with 9-methyl substitution (III and IV). In III there is an axial-methyl against axial-fluorine interaction which increases the equilibrium constant between the forms to 0·95 compared with 0·35 for I $\rightleftharpoons$ II. It is interesting that the axial-methyl *v.* axial-fluorine and axial-ring CH_2 *v.* axial-fluorine interactions are pretty much at stand-off in III and IV as far as energy effects are concerned and produce similar but, not identical, chemical-shift differences of 544 and 397 c/s.

Substitution of a methyl group at other than the 9- or 10-position of *cis*-decalin leads to a strong unbalancing of the forms corresponding to I or II since the methyl will in general be much more favourably located in one form than in the other. Such effects have been observed with the 1-, 3-, and 6-methyl-2,2-difluoro-*cis*-decalins, all of which give spectra corresponding to a single conformation with negligible changes in the equatorial-axial fluorine chemical-shift differences over a 100° or more temperature variation. As expected, the same behaviour is observed with 2,2-difluoro-*trans*-decalin which also has only one favourable conformation.

The very large axial-fluorine, equatorial-fluorine chemical-shift difference observed with 1- and 3-methyl substitution is especially interesting in that it is substantially larger than the observed shift difference with 1,1-difluorocyclohexane (884 c/s). This may be due to a neighbouring-group electrical effect or possibly a steric effect of the methyl



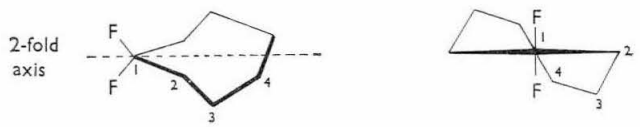
group, which because of its position in the favourable conformation may act to spread the F–C–F bond angle. The latter notion fits in with the 1175 c/s shift difference calculated for the stable conformer of 1,1-difluoro-3-phenyl cyclobutane,[12] wherein the F–C–C bond angle is expected to be larger than the normal value because of the strained ring. Furthermore, the steric interferences which in I—VI lead to decreases in the fluorine chemical-shift differences are of types expected to act as to tend to decrease the F–C–F bond angle.

The general success of the fluorine-labelling technique in dealing with cyclohexane and fused cyclohexane ring systems has inspired an attack on determining the conformations and rates of conformational equilibration of cycloheptane which are much less familiar and less well understood than those of cyclohexane. There is little definitive experimental evidence on the favoured conformation of the cycloheptane ring and, indeed, the most helpful work which is so far available is the excellent theoretical study by Hendrickson[11b,13] wherein a number of interesting *a priori* predictions were made about the relative stabilities of the various reasonably possible conformations of cycloheptane and substituted cycloheptanes.

A very striking feature of cycloheptane, which is most clearly evident from molecular models, such as the Dreiding or Fieser models, which have free rotation about C–C bond axes, is the general limberness of the ring. There is no conformation like the chair form of cyclohexane which is rigid so long as no bending of the C–C–C angles from their normal values is allowed. This suggests that conformational equilibration of a type which would interchange the

relative positions of *gem* substituents might well occur with substantially greater ease than with cyclohexane. Consequently, it is perhaps not surprising that 1,1-difluorocycloheptane (VII) shows no chemical-shift difference between the fluorines at room temperature or all the way down to −180° (Fig. 5).[14]

The failure to observe a chemical-shift difference between the fluorines of VII at very low temperatures might be taken to indicate that inversion is rapid but there is another possibility which has to be considered, namely that the fluorines could be in a conformation in which they would be equivalent by symmetry and hence unable to show a chemical-shift difference, no matter how low the temperature. This is particularly important with the twist-chair form which has an axis of symmetry passing through a carbon atom and the bond opposite (VIII). If the fluorines were located most favourably at the 1- or

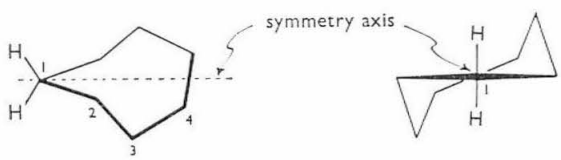


VIII

axis position of VIII, they would be equivalent by symmetry and, to determine whether this is a likely possibility, we may consider Hendrickson's calculations[13] wherein the interacting energy of a methyl group has been evaluated for each position of the twist-chair conformation (Table V). It will be noted that, except for the 1-position, there are equatorial-like and axial-like configurations of a substituent group at each of the carbons. The difference in energy between the various equatorial positions is quite small and all are substantially more favourable than the axial-like positions. If we assume that the interaction energy associated with *gem* substitution is the simple sum of the separate energies for each position, then clearly the most favourable conformation for *gem* substitution will be the one with the groups at the axis position. Two fluorines

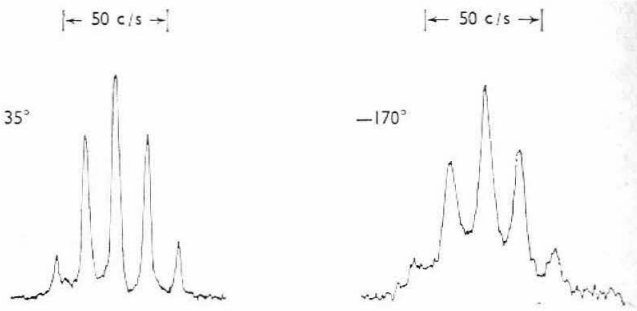
TABLE V

CALCULATED ENERGIES (KCAL/MOLE) RESULTING FROM METHYL SUBSTITUTION ON THE TWIST-CHAIR FORM OF CYCLOHEPTANE (HENDRICKSON)



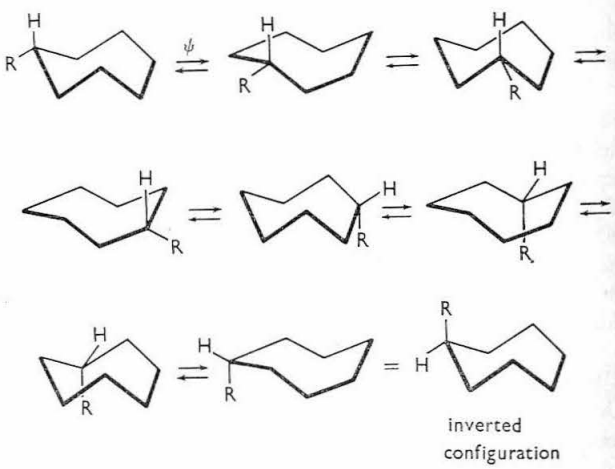
	mono	gem
1 (axis)	0·03	0·06
2e	−0·01	
2a	4·27	4·26
3e	0·00	
3a	4·88	4·88
4e	0·01	
4a	1·43	1·44

FIG. 5. Change in ^{19}F magnetic resonance spectra of 1,1-difluorocycloheptane between 35° and −170°.



at this position would be equivalent and show no chemical-shift difference.

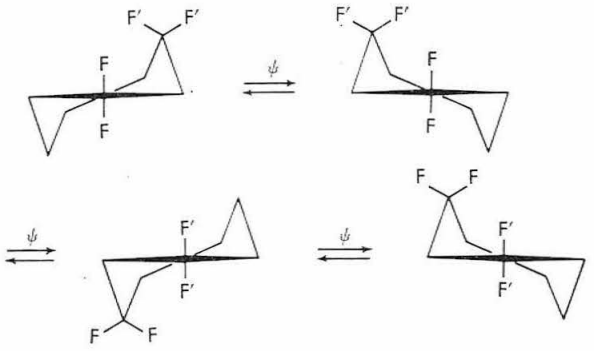
There are two other modes whereby *gem*-fluorines could be equivalent. One is a more or less conventional inversion whereby the chair (or twist chair) goes to the boat and to a new chair in much the same manner as postulated for cyclohexane. The other possible mode of inversion is that discussed by Hendrickson whereby a twist-chair to chair to twist-chair interconversion (pseudorotation, ψ) causes a substituent group to travel around the ring and undergo inversion of configuration whenever the carbon carrying the group goes through the axis position[15] of the twist-chair form. The sequence of changes for the chair forms is shown below.



Pseudorotation is expected to be an especially favourable way of achieving inversion because Hendrickson's calculations show that the twist-chair form is but 2 kcal/mole more stable than the chair form. Since the chair forms are expected to be the least favourable point on the pseudorotation 'itinerary',[13] the activation energy for inversion by pseudorotation should not be much more than 2 kcal/mole, even for a *gem*-fluoro compound. The relatively slight changes in steric interactions which occur in pseudorotation are best seen by actual manipulation of models, preferably of the Fieser–Dreiding type.

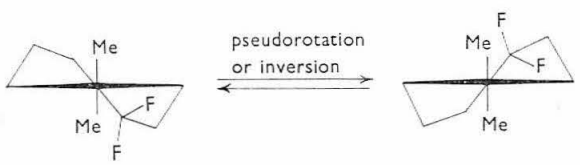
To distinguish betwixt the possible modes of achieving equivalent fluorines we have studied some substituted

gem-fluorocycloheptanes.[14] Consider 1,1,3,3-tetrafluorocycloheptane (IX). With this compound we expect at



IX

least one pair of fluorines to be nonequivalent unless pseudorotation (or inversion) is very facile, because no more than two fluorines can be on an 'axis' position[15] at any one time. The fact is that the fluorines of IX show no magnetic nonequivalence to −180°. We can therefore conclude that pseudorotation and/or ring inversion is fast even at this temperature. Some help in distinguishing between these two possibilities is provided by 1,1-difluoro-4,4-dimethylcycloheptane. With this compound, the methyl groups, being larger than fluorine, are expected to occupy the axis positions[15] which would make the fluorines take nonequivalent equatorial and axial locations at the 1-position unless pseudorotation or inversion occurs.



X

With *gem* methyls, pseudorotation should be far less favourable than for cycloheptane itself because the chair form with an inside methyl group is expected to have a cross-ring steric repulsion of 9·6 kcal/mole.[12]

Interestingly, 1,1-difluoro-4,4-dimethylcycloheptane does show a striking change in its n.m.r. spectrum at low temperatures, see Fig. 6. At and below −163°, the fluorine chemical-shift difference is 840 c/s and the general appearance of the spectrum indicates the presence of equatorial-like and axial-like fluorines (compare with Fig. 1). Preliminary analysis of the rate of change of the line shapes as a function of temperature indicate an E_a value of about 6 kcal/mole for the process which interchanges the fluorines. Since this is so substantially less than the calculated 9·6 kcal/mole for pseudorotation, we conclude that it is likely that the interchange results from ring inversion for this particular system while the exceedingly rapid exchange in 1,1,3,3-tetrafluorocycloheptane involves pseudorotation.

Although the value of the fluorine-labelling technique for studying conformational equilibria and equilibration

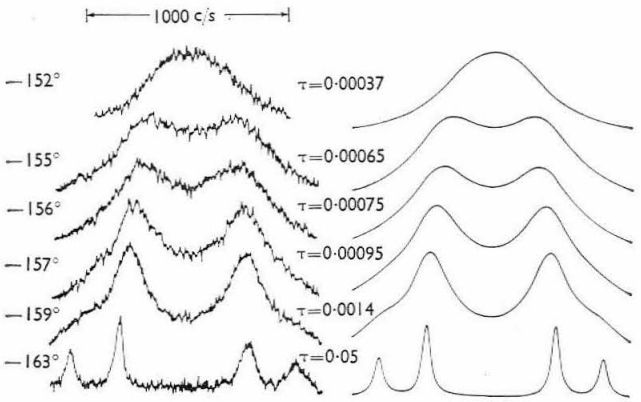


FIG. 6. Changes in experimental and calculated ^{19}F spectra of 1,1-difluoro-4,4-dimethylcycloheptane as a function of inversion rate.

by n.m.r. spectroscopy still remains to be established by additional point-to-point checks with non-fluorine-containing compounds, the evidence so far obtained does indicate that the method has considerable advantages and may be of wide applicability.

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15. This position is not really an *axis position* when the ring is asymmetrically substituted because there can be no axis of symmetry for such compounds. Inversion occurs when the substituent(s) pass through the 1-position of VIII.